Channels and Life, a Brief Introduction

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Almost all of life occurs inside cells in salt water that resembles the oceans of the earth billions of years ago, rich in potassium chloride. Cells live in another kind of salt water, rich in sodium chloride, that resembles the oceans of today. The imbalance of these salts creates physical conditions that require special proteins, channels and their close cousins transporters, if the cell is to remain viable and not swell and explode. These special proteins are as old as animal cells themselves. Without them, cells must be have rigid walls like plants, and organisms made of such rigid cells do not move easily and so are limited in what they can do.

Channel proteins are valves that control the movement of salts across cell membranes. The salts are atoms some 2 Å in diameter (chiefly Na^+, K^+, Ca^{2+} and Cl^- ions) that carry electrical charge. These ions exert strong electrical forces, maintaining a resting voltage across nearly every cell in the body (the red cell being the notable exception). Channels are valves that control the movement of electrical charge, salts, and water across otherwise impermeable membranes that block the movement of almost everything else. Without channels, membranes would block nearly all flow and cells would soon starve to death, or drown in their waste.

Cells contain proteins typically 50 Å in diameter consisting of say 100,000 atoms that do most of the work of life. Proteins are macromolecular machines very much bigger than ions like Na^+ and so proteins cannot cross membranes by themselves. Proteins require specialized transport systems which package the proteins inside mini-cells called vesicles surrounded by their own membranes. Cells are bags that contain enormous numbers of these vesicles. Much work has been done on the movement of vesicles in and through cells and the role of proteins in that movement.

The work proposed here concerns the protein valves that control the movement of ions through membranes, both the membranes of cells and those of vesicles. These ion channels make up something like one third of all the proteins of life and control an enormous range of living processes. The flow of ions triggers contraction of muscle, including the skeletal muscles that allow us to move, and the flow of ions that coordinates the contraction of cardiac muscle so the heart can function as a pump. Ion channels control the production of urine, the secretion of hormones and an enormous range of life's functions including the fusion and movement of vesicles across cell membranes (and I suspect across intracellular membranes as well, although that is not yet proven, as far as I know). A large fraction of all drugs act on channel proteins.

Ion channels were discovered (en masse) in the 1950's as the molecules that control signaling in the nervous systems, that control the action potential, and its propagation along nerve fibers and at synapses connecting one nerve cell with another or with a muscle fiber. In fact, vesicles were first extensively studied in synapses, nerves, and muscles. The fusion of vesicles in the presynaptic cell to the synaptic membrane is responsible for the release of transmitters (like acetylcholine) that diffuse to the postsynaptic cell, where the transmitter binds to a chemically activated channel (e.g., the acetylcholine channel) which opens, and initiates the postsynaptic action potential. The fusion of vesicles to synaptic membranes is controlled by (presynaptic) calcium channels and in fact vesicle fusion was extensively studied in this context in the 1950s leading to at least two Nobel Prizes (Bernard Katz and John Eccles). Channels control the signal

(calcium current) that initiates presynaptic vesicle fusion and different channels produce the resulting postsynaptic signal itself. Ion channels are as important at most steps of the vesicle process at synapses as they are in the signaling process in nerves and muscles.

Ion channels have been recognized as (nearly) universal controllers of life — important in many cells other than nerves and muscles — only in the last 10 years or so after the discovery of the ABC proteins and TRP channels and transporters. But one area where their role is not fully understood is in the control of protein and vesicle transport across membranes *within* cells.

Our work is on a smaller scale than cells or even vesicles. We study how ions move inside proteins. We are concerned with ions typically 50-200× smaller than proteins and 1,000-10,000× smaller than vesicles. We seek to understand how individual atoms of Na^+, K^+, Ca^{2+}, Cl^- move through single channel proteins along with the water surrounding these atoms.

The flow of these ions carries electrical current and so produces the signals of the nervous and muscular systems. The flow of ions through channels is regulated by the opening and closing of channel proteins. Channel proteins are valves that open and close to allow certain ions through. Each channel type has its own control mechanism for opening and closing. The channels of nerve membranes and presynaptic terminals are opened and closed by voltage. Some channels of postsynaptic nerve cells respond not to voltage but to chemicals (e.g., acetylcholine) secreted by the fusion of vesicles to the cell membranes of presynaptic cells. A few channels are locked open and never close: among these are perforin (that I call the killer channel) used by T cells of the immune system to kill cancer cells and other cellular threats to animal existence.

We are interested in the mechanism by which channels open and close. The mechanism of opening and closing of valves is as fundamental to life as the mechanism of valves is to the plumbing systems of our water technology, or as the switching of transistors is to our information computer technology. Transistors are valves for electrical current and open and close to carry the bits and bytes that are the words of computers.

Protein channels are known to open (and close) very quickly (faster than 1 microsecond). Each of the thousands of channel types has its own mechanism to modulate and control this sudden opening and closing but all channels seem to open and close in a similar way. The modulation is very different in different types of channels. The opening and closing is very similar in thousands of types of channels. The physical mechanism by which channels open and close is a common denominator of channel function, and thus a common denominator of life.

We have proposed a physical mechanism of opening and closing in a theoretical paper. The physical mechanism was the formation of a void—a nanobubble—inside a channel protein. Following extensive previous work on water in capillaries, we proposed that water can pull away from the wall of a channel protein leaving a void through which ions cannot move. The formation of voids like these is well known on the macroscopic scale and is a major technological problem. Bubbles are very hard to remove from pipes and tubes a few millimeters in diameter. We propose that these bubbles also form on the atomic scale inside channel proteins, including inside the proteins that control vesicles. Our nanobubbles are say 3 Å in diameter, very much smaller than the vesicles themselves (which also confusingly can look like bubbles but are typically 500–1,000× larger).

We propose to study this common denominator of channel opening and closing (widely called ‘gating’ for short) using an array of physical techniques including mathematical models and optical measurements. We propose to study the interactions of dissolved gases with gating mechanisms to show how dissolved gases can move into voids, filling our nanobubbles, and interfering with gating, thus producing anesthesia by gases.